## Cost-effectiveness of the psycho-educational blended (group and online) intervention HypoAware compared with usual care for people with Type 1 and insulin-treated Type 2 diabetes with problematic hypoglycaemia

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## Research: Educational and Psychological Aspects

# Cost-effectiveness of the psycho-educational blended (group and online) intervention HypoAware compared with usual care for people with Type 1 and insulin-treated Type 2 diabetes with problematic hypoglycaemia: analyses of a cluster-randomized controlled trial

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## Abstract

**Aims** To evaluate the cost-effectiveness of HypoAware, a blended (group and online) psycho-educational intervention based on the evidence-based Blood Glucose Awareness Training, in comparison with usual care in people with Type 1 and Type 2 diabetes with a high risk of severe hypoglycaemia.

**Methods** We performed an economic evaluation, from a societal and healthcare perspective, that used data from a 6-month, multicentre, cluster-randomized controlled trial ($n$ = 137).

**Results** The proportion of people with at least one severe hypoglycaemic event per 6 months was 0.22 lower (95% CI –0.39 to –0.06) and the proportion of people with impaired hypoglycaemia awareness was 0.16 lower (95% CI –0.34 to 0.02) in the HypoAware group. There was no difference in quality-adjusted life-years (–0.0; 95% CI –0.05 to 0.05). The mean total societal costs in the HypoAware group were EUR708 higher than in the usual care group (95% CI –951 to 2298). The mean incremental cost per severe hypoglycaemic event prevented was EUR2,233. At a willingness-to-pay threshold of EUR20,000 per event prevented, the probability that HypoAware was cost-effective in comparison with usual care was 54% from a societal perspective and 55% from a healthcare perspective. For quality-adjusted life-years the incremental cost-effectiveness ratio was EUR119,360/quality-adjusted life-year gained and the probability of cost-effectiveness was low at all ceiling ratios.

**Conclusions** Based on the present study, we conclude that HypoAware is not cost-effective compared to usual care. Further research in less well-resourced settings and more severely affected patients is warranted. (Clinical Trials Registry no: Dutch Trial Register NTR4538.)

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## Introduction

Severe hypoglycaemia is the major adverse event related to insulin treatment in people with Type 1 diabetes and people with insulin-treated Type 2 diabetes,. The estimated average incidence of severe hypoglycaemia ranges from 1.0 to 1.7 events per patient per year. Most incidents occur in people with Type 1 diabetes [1–3]. Longer disease duration (>15 years) is associated with an increase in the incidence of severe hypoglycaemia to 3.2 events per patient per year [4]. With progressive insulin deficiency, the frequency of severe hypoglycaemic events in people with Type 2 diabetes is similar to that in those with Type 1 diabetes because the sulfonylurea or insulin treatment they receive increases the risk of hypoglycaemia [5]. Hypoglycaemia causes significant morbidity, reduced quality of life and increased mortality [6–8], and leads to high societal costs. Severe hypoglycaemia-related costs consist of increased healthcare utilization

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**What's new?**

- We have evaluated the cost-effectiveness of HypoAware, a blended (group and online) psycho-educational intervention based on the evidence-based Blood Glucose Awareness Training, in comparison with usual care in people with diabetes with a high risk of severe hypoglycaemia.
- HypoAware was not cost-effective from a societal perspective in comparison with usual care. Further research in less well-resourced settings and more severely affected patients is warranted.

(emergency room visits, ambulance costs, hospital admissions, outpatient visits) and work absenteeism. It is estimated that for each severe hypoglycaemic event requiring medical assistance the healthcare costs are EUR2,100 and lost productivity costs are EUR1,000 [6,9].

Psycho-educational interventions, such as Blood Glucose Awareness Training (BGAT), aimed at reducing and preventing hypoglycaemia, are evidence-based [10], but demanding both on clinics' resources as well as participants' time as a result of the relatively high number of group sessions and extensive homework assignments. To date, no economic evaluations of BGAT-like programmes have been conducted. Given the scarce resources available for healthcare, evidence that cost-effective interventions lower hypoglycaemia risk in diabetes is urgently needed. We therefore developed a brief blended group intervention, HypoAware, based on key ingredients of BGAT. We reduced the number of group sessions to three 2.5-h sessions, combined with an online learning environment to maintain quality and improve attractiveness and comprehensibility, while keeping resources (and thus costs) at a minimum. In a multicentre pilot study of HypoAware in people with Type 1 and Type 2 diabetes and problematic hypoglycaemia, we demonstrated feasibility and acceptability [11]. In addition, we conducted a randomized controlled trial (RCT) and reported on the clinical effectiveness, showing fewer severe hypoglycaemic events, significantly improved hypoglycaemia awareness and less hypo-distress compared with usual care [12].

In the present paper, we examined the cost-effectiveness of the psycho-educational intervention HypoAware in people with Type 1 and Type 2 diabetes who were at high risk of hypoglycaemic events, and compared this with usual care, from a societal and healthcare perspective. From the societal perspective, all relevant costs were taken into account, that is healthcare utilization, patient and lost productivity costs. Although the societal perspective is recommended by the Dutch National Healthcare Institute in view of healthcare reimbursements [13], other national institutes such as the National Institute for Clinical Excellence (NICE) recommend a healthcare perspective, which only includes healthcare utilization costs [14]. Quality-adjusted life-years (QALYs) were included as an outcome measure next to the clinical outcome measures of the trial, because decision-makers need this information to be able to compare the cost-effectiveness of HypoAware with other new interventions for diabetes or other health conditions [15].

## Participants and methods

An economic evaluation was performed from a societal and healthcare perspective alongside a two-arm multicentre, cluster-RCT with follow-up measurements at 2, 4 and 6 months conducted at eight self-selected outpatient diabetes clinics in the Netherlands. The full design of the trial is described elsewhere [16]. Cluster randomization was carried out prior to recruitment of participants at the level of the participating clinics to avoid contamination between treatment groups within the clinics.

The study protocol was approved by the Ethics Committee of the VU University Medical Centre, certified by the Central Committee on Research involving Human Subjects in the Netherlands (NL47354.029.13, registration number 2014.007). We obtained written informed consent from all participants.

### Participants

In short, people were eligible for this study if they: were aged ≥18 years; were treated for Type 1 or Type 2 diabetes in an outpatient setting; performed at least three insulin injections a day or were on continuous subcutaneous insulin infusion; and had a high risk of severe hypoglycaemia (one or more severe hypoglycaemic events in the past 2 years and/or impaired awareness of hypoglycaemia according to Gold *et al.* (a score of ≥4) [17].

The main exclusion criteria were: serious medical comorbidity; major psychiatric disorder; pregnancy; insufficient Dutch language skills; and visual impairment.

### Intervention group: HypoAware

HypoAware consists of three group sessions of 2.5 h over a period of 4 weeks, combined with two online modules in the weeks between meetings. Groups are led by two trained diabetes professionals and consist of eight participants. HypoAware aims to improve symptom recognition and risk awareness, provide preventive and problem-solving strategies, and help the individual cope with (the risk of) hypoglycaemia. More details can be found elsewhere [11].

### Control group: usual care

Participants in the control group received usual care provided by their diabetes team: a 10-min consultation with their

endocrinologist every 3 to 6 months (depending on the clinic's protocol) and additional 45-min consultations with their diabetes nurse, if needed. After the 6 month follow-up, participants in the control group were offered HypoAware.

### Outcomes

All measures were administered at the start, and 2, 4 and 6 months after baseline using web-based questionnaires.

Severe hypoglycaemic events were defined as those serious enough to require the help of another person. We evaluated the proportion of participants who had experienced one or more severe hypoglycaemic event during the study period of 6 months. Whether those events needed medical assistance was assessed using the TiC-P questionnaire (Trimbos/iMTA questionnaire for costs associated with psychiatric illness; see below).

We determined the proportion of participants with impaired hypoglycaemia awareness using the one-item scale proposed by Gold *et al*. [17]. A score of ≥4 indicates impaired hypoglycaemia awareness. QALYs were estimated using the EuroQoL five dimensions, five levels questionnaire (EQ-5D-5L) as recommended by NICE [14,18]. The self-reported EQ-5D-5L health states were converted to utility scores using the Dutch EQ-5D-5L tariff [19]. QALYs were subsequently calculated by multiplying the utility score belonging to a health state by the time spent in that health state. Changes in utility scores between two assessments were linearly interpolated. QALYs were also calculated using the participants' ratings on the visual analogue scale included in the EQ-5D-5L, using the methodology described above.

Costs were measured from a societal perspective using an adapted version of the TiC-P questionnaire [20] with a recall period of 2 months at 2, 4 and 6 months. Included were costs of healthcare utilization (i.e. hospital admissions, outpatient visits and calls, emergency room visits, ambulance transfers, medication and medical supply usage), costs of informal care, and lost productivity costs (reduced productivity from paid and unpaid work). When available, Dutch guideline prices were used to value resource use (http://www.zorginstituutnederland.nl). Medication use was valued using Royal Dutch Society for Pharmacy prices [21]. Lost productivity costs were calculated according to the friction cost approach using sex-specific incomes of the Dutch population [22]. According to the friction cost approach, a sick employee is replaced after a certain amount of time (friction period: 84 days in the Netherlands) after which there are no more lost productivity costs. All costs were adjusted to the year 2015 using consumer price indices.

### Statistical analysis

Both cost-effectiveness and cost-utility analyses were performed with a time horizon of 6 months; therefore, discounting was not necessary. All analyses were intention-to-treat. Missing cost and effect data were imputed using multiple imputation with chained equations [23]. To account for the skewed distribution of costs, predictive mean matching was used in the multiple imputation with chained equations procedure [24]. An imputation model was created including variables that differed between groups at baseline, baseline characteristics that were related to missingness of cost and effect outcomes at 6 months follow-up, and baseline characteristics that were associated with cost and effect outcomes at 6-month follow-up (sex, age, nationality, education, employment, marital status, comorbidity, diabetes duration, $HbA_{1c}$, number of severe hypoglycaemic events in the past 6 months and in the past 2 years, Gold score, diabetes complications, diabetes treatment, and type of diabetes). The number of imputed datasets was increased until the loss of efficiency was lower than 5% [24]; in this study, 20 imputed datasets were needed. The imputed datasets were analysed separately as described below, and subsequently results were pooled using Rubin's rules [25].

Aggregated and disaggregated costs were calculated, and 95% CIs around cost differences were estimated using bias-corrected accelerated bootstrapping (5000 replications) [26]. Bootstrapping was used because costs are generally heavily skewed to the right.

In the cost-effectiveness analyses, cost and effect differences were estimated using seemingly unrelated regression. The seemingly unrelated regression model consists of several linear regression equations with different dependent and explanatory variables, where the error terms in the different regression equations are correlated [27]. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in costs between the groups by the difference in effects. Statistical uncertainty surrounding the ICERs was estimated using bias-corrected accelerated bootstrapping (5000 replications). Bootstrapped cost-effect pairs were plotted in cost-effectiveness planes [28]. In a cost-effectiveness plane, effect differences are plotted on the *x*-axis and cost differences on the *y*-axis, resulting in four quadrants: the northeast quadrant indicating that the HypoAware intervention is more effective and associated with higher costs than usual care; the southeast quadrant indicating that the intervention is more effective and associated with lower costs; the southwest quadrant indicating that the intervention is less effective and associated with lower costs; and the northwest quadrant indicating that the intervention is less effective and associated with higher costs.

Cost-effectiveness acceptability curves show the probability that the HypoAware intervention is cost-effective in comparison with usual care (*y*-axis) at different ceiling ratios (*x*-axis) [29]. The ceiling ratio is defined as the maximum amount of money that society is willing to pay to gain one unit of effect extra, e.g. one QALY gained or one severe hypoglycaemic event prevented.

Two sensitivity analyses were performed. In the first sensitivity analysis, analyses were performed from a

 

healthcare perspective, meaning that only healthcare utilization costs were taken into account. In the second sensitivity analysis, analyses were restricted to participants with Type 1 diabetes.

## Results

### Participants

Participants were recruited by their treating endocrinologist or diabetes nurse. We have no records of the number of participants invited. Baseline measurement was completed by 137 participants (Table 1): 66 participants (48%) in the control group and 71 participants (52%) in the intervention group. Full details of participant flow are described elsewhere [12].

### Clinical outcomes

Table 2 shows the clinical outcomes. Participants in the intervention group reported, on average, 0.32 fewer events of severe hypoglycaemia per 6 months than participants in the usual care group (95% CI –5.4 to 4.8). The proportion of participants with at least one event of severe hypoglycaemia was 0.22 lower in the intervention group than in the control group (95% CI –0.34 to –0.06). The proportion of participants with impaired hypoglycaemia awareness was 0.16 lower in the intervention group (95% CI –0.34 to 0.02). The mean number of QALYs based on the EQ-5D-5L dimensions and thermometer did not differ between the two groups.

**Table 1** Baseline demographic and clinical characteristics of the participants

| | Usual care ($n$ = 66) | HypoAware ($n$ = 71) |
|---|---|---|
| Age, years | 51.3 (14.0) | 52.7 (12.4) |
| Female, $n$ (%) | 29 (44) | 34 (48) |
| Employed, $n$ (%) | 37 (56) | 37 (52) |
| Education, $n$ (%) | | |
| Primary | 16 (24) | 23 (32) |
| Secondary | 30 (46) | 20 (28) |
| Higher | 20 (30) | 28 (39) |
| Type diabetes, $n$ (%) | | |
| Type 1 diabetes | 59 (91) | 62 (87) |
| Type 2 diabetes | 6 (9) | 8 (11) |
| Other (MODY) | 1 (2) | 1 (1) |
| Treatment, $n$ (%) | | |
| CSII | 36 (55) | 29 (41) |
| MDI | 30 (46) | 42 (59) |
| Comorbidity, $n$ (%) | 33 (50) | 40 (56) |
| $HbA_{1c}$, mmol/mol | 60.4 (12.2) | 60.8 (11.2) |
| $HbA_{1c}$, % | 7.7 (1.1) | 7.7 (1.0) |
| Diabetes duration, years | 27.5 (13.1) | 24.6 (14.0) |
| Complications, $n$ (%) | 28 (42) | 29 (41) |
| Non-severe hypoglycaemic events per week (<4 mmol/l / <72 mg/dl)* | 7.4 (3.9) | 5.3 (3.8) |
| Impaired hypoglycaemia awareness (Gold *et al.* [17]), $n$ (%) | 48 (73) | 56 (79) |
| Severe hypoglycaemic events in the previous 6 months | 1 (0–5) | 2 (0–6) |

Data are mean (SD) or median (interquartile range), unless otherwise indicated.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; MODY, maturity onset diabetes of the young.
*In participants without real-time continuous glucose monitoring at T1 (total $n$ = 98; control $n$ = 45; intervention $n$ = 53).
Adapted from original article [12].

### Costs

The mean total societal costs in the intervention group were EUR708 higher than in the usual care group (95% CI –951 to 2,298; Table 2), but this difference was not statistically significant. Healthcare costs were non-significantly lower in the intervention group than in the usual care group (mean difference: EUR–197, 95% CI –876 to 424).

The only costs that differed significantly between both groups were diabetes costs (insulin, blood glucose test strips and sensors), which were EUR348 lower in the HypoAware group (95% CI –673 to –30), and costs of unpaid work (such as cleaning, cooking, picking up children), which were EUR 1,094 higher in the HypoAware group (95% CI 529 to 1,876).

### Cost-effectiveness

The ICER for the number of severe hypoglycaemic events was EUR2,233/severe hypoglycaemic event prevented (Table 3), meaning that to prevent one event of severe hypoglycaemia 2,233 EUR should be invested in the HypoAware group as compared with the usual-care group. Forty percent of the bootstrapped ICERs were situated in the north-east quadrant of the cost-effectiveness plane (Fig. 1a), indicating that the intervention was, on average, more effective in preventing severe hypoglycaemic events, but was associated with higher costs than usual care. The cost-effectiveness acceptability curve (Fig. 1b) shows that the probability that the intervention was cost-effective in comparison with usual care was 0.24 at a willingness to pay of EUR0 per severe hypoglycaemic event prevented, and that this increases to a probability of 0.54 at a willingness to pay of EUR20,000 per severe hypoglycaemic event prevented.

The probability of the intervention being cost-effective in comparison with usual care in preventing one participant having at least one severe hypoglycaemic event was 0.24 and 0.95 at willing-to-pay values of 0 and EUR15,000/hypoglycaemic event prevented, respectively (Fig. 2a and b). For hypoglycaemia unawareness, this probability was 0.24, 0.91 and 0.95 at willing-to-pay values of 0, EUR20,000 and EUR84,000/participant with impaired awareness of hypoglycaemia prevented, respectively. Finally, for cost utility, this probability was 0.24 and 0.27 at willing-to-pay values of EUR0 and EUR20,000/QALY gained, respectively (Fig. 3a

**Table 2** Mean outcomes and costs in 2015 Euros in both the HypoAware intervention and usual care groups, and mean differences (95% CIs) between groups

| Outcome | HypoAware Mean (SE) | Usual care Mean (SE) | Difference (95% CI) |
|---|---|---|---|
| Clinical outcomes | | | |
| Number of severe hypoglycaemic events | 6.9 (2.1) | 7.3 (1.4) | −0.32 (–5.4; 4.8) |
| Proportion of participants with a severe hypoglycaemic events | 0.59 (0.07) | 0.81 (0.05) | –0.22 (–0.39; –0.06) |
| Proportion of unaware participants | 0.56 (0.07) | 0.72 (0.06) | –0.16 (–0.34; 0.02) |
| QALYs | 0.34 (0.02) | 0.34 (0.02) | –0.00 (–0.05; 0.05) |
| QALY (visual analogue scale) | 0.33 (0.01) | 0.34 (0.01) | –0.01 (–0.04; 0.02) |
| Costs, EUR, 2015 | | | |
| Healthcare costs | 1896 (281) | 2093 (297) | |
| Primary care costs | 328 (58) | 209 (34) | 119 (2; 242) |
| Secondary care costs | 997 (204) | 1138 (241) | –141 (–715; 284) |
| Diabetes costs | 398 (140) | 746 (147) | –348 (–673; –30) |
| Intervention costs | 173 (0) | NA | NA |
| Informal care costs | 427 (111) | 437 (186) | –9 (–623; 265) |
| Lost productivity costs | 2459 (634) | 1545 (382) | 914 (–146; 2017) |
| Unpaid work | 1532 (487) | 438 (100) | 1094 (529; 1876) |
| Absenteeism costs | 499 (286) | 881 (340) | –383 (–1220; 153) |
| Presenteeism costs | 428 (142) | 225 (65) | 203 (–17; 478) |
| Total societal costs | 4783 (748) | 4075 (625) | 708 (–951; 2298) |

NA, not applicable; QALY, quality-adjusted life year.

and b). For QALYs based on the EQ-5D-5L thermometer, these probabilities were similar (Table 3).

### Sensitivity analyses

When only healthcare costs were taken into account, costs in the intervention group were non-significantly lower than in the usual care group (mean difference: – EUR197, 95% CI – 876 to 424), whereas societal costs were non-significantly higher (Table 2). As compared to the main analysis, the probabilities of HypoAware being cost-effective in comparison with usual care were higher in this sensitivity analysis. In particular, the cost-effectiveness acceptability curve shows that the probability that the intervention was cost-effective in comparison with usual care in preventing one severe hypoglycaemic event was 0.69 at a willingness to pay of EUR0/severe hypoglycaemic event prevented and that this decreases to a probability of 0.55 at a willingness to pay of EUR20,000/severe hypoglycaemic event prevented (Table 3). To prevent one participant having at least one severe hypoglycaemic event, the probability of the intervention being cost-effective in comparison with usual care was 0.69 and 0.95 at willing-to-pay values of 0 and EUR2,400/hypoglycaemic event prevented, respectively. For hypoglycaemia unawareness, this probability was 0.69 and 0.97 at willing-to-pay values of 0 and EUR3,900/participant with impaired hypoglycaemia awareness, respectively. Finally, for cost utility, this probability was 0.69 and 0.60 at willing-to-pay values of 0 and EUR20,000/QALY gained, respectively.

Sensitivity analyses among people with Type 1 diabetes showed few differences compared with the total population (Table 3). Societal costs were higher (mean difference: EUR1,094, 95% CI –562 to 2749), but still non-significant.

## Discussion

We conducted a multicentre trial to evaluate the cost-effectiveness of HypoAware, a brief blended (online and face-to-face) psycho-educational group intervention based on BGAT in a sample of insulin-treated people with problematic hypoglycaemia.

Total societal costs in the HypoAware group were EUR708 higher than in the usual care group, but not statistically significant. From a societal perspective, the probability that the intervention was cost-effective in comparison with usual care was 0.54 at a willingness to pay of EUR20,000/severe hypoglycaemic event prevented. For QALYs, the maximum probability that HypoAware was cost-effective in comparison with usual care was 0.27.

There was no significant difference between the intervention and usual care groups in effects on severe hypoglycaemic events, proportion of participants with impaired awareness of hypoglycaemia and QALYs, but we did find a significant difference in proportion of participants with at least one event of severe hypoglycaemia. Improvement in events of severe hypoglycaemia follows improvement in hypoglycaemia awareness; this may translate into less severe hypoglycaemic events in the long term. From a healthcare perspective, costs were lower in the HypoAware group compared with the usual care group (EUR–197, 95% CI – 876 to 424), and the probability that the intervention was cost-effective in comparison with usual care was 0.60 at a willingness to pay of EUR20,000/QALY; however, when interpreting the results of the study, one should take into account that uncertainty is considerable, as shown by the wide 95% CIs and the considerable spread of bootstrapped cost-effect pairs in the cost-effectiveness plane. Also, the wide

**Table 3** Results of the cost-effectiveness analyses

| Outcome | Cost difference in EUR (95% CI) | Effect difference (95% CI) | ICER | Distribution cost-effectiveness plane, % | | | | *P** | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | North-east | South-east | South-west | North-west | Willingness to pay = 0 | Willingness to pay = 20,000 |
| Main analysis | | | | | | | | | |
| Number of severe hypoglycaemic events prevented | 708 (–951; 2298) | 0.32 (–4.8; 5.4) | 2233 | 40 | 15 | 8 | 37 | 0.24 | 0.54 |
| Participants with a severe hypoglycaemic event prevented, % | 708 (–951; 2298) | 0.22 (0.06; 0.39) | 3182 | 77 | 23 | 0 | 0 | 0.24 | 0.98 |
| Unaware participants prevented, % | 708 (–951; 2298) | 0.16 (–0.02; 0.34) | 4437 | 74 | 22 | 1 | 4 | 0.24 | 0.88 |
| QALYs | 708 (–951; 2298) | –0.00 (–0.05; 0.05) | –888936 | 36 | 13 | 10 | 41 | 0.24 | 0.27 |
| QALYs (visual analogue scale) | 708 (–951; 2298) | –0.01 (–0.04; 0.02) | –83112 | 21 | 10 | 14 | 56 | 0.24 | 0.30 |
| Healthcare perspective | | | | | | | | | |
| Number of severe hypoglycaemic events prevented | –197 (–886; 420) | 0.32 (–4.8; 5.4) | –621 | 15 | 40 | 29 | 16 | 0.69 | 0.55 |
| Participants with a hypoglycaemic event prevented, % | –197 (–886; 420) | 0.22 (0.06; 0.39) | –886 | 31 | 69 | 0 | 0 | 0.69 | 1.0 |
| Unaware participants prevented, % | –197 (–886; 420) | 0.16 (–0.02; 0.34) | –1234 | 30 | 66 | 3 | 1 | 0.69 | 0.97 |
| QALYs | –197 (–886; 420) | –0.00 (–0.05; 0.05) | 247388 | 13% | 36 | 33 | 18 | 0.69 | 0.60 |
| QALYs (visual analogue scale) | –197 (–886; 420) | –0.01 (–0.04; 0.02) | 23130 | 6% | 25 | 44 | 25 | 0.69 | 0.31 |
| Type 1 diabetes | | | | | | | | | |
| Number of severe hypoglycaemic events prevented | 1094 (–562; 2749) | –0.71 (–5.9; 4.5) | –1549 | 33 | 7 | 6 | 54 | 0.14 | 0.39 |
| Participants with a severe hypoglycaemic event prevented, % | 1094 (–562; 2749) | 0.20 (0.02; 0.37) | 5575 | 85 | 13 | 1 | 1 | 0.14 | 0.92 |
| Unaware participants prevented, % | 1094 (–562; 2749) | 0.19 (–0.00; 0.38) | 5686 | 84% | 13% | 0% | 2% | 0.14 | 0.89 |
| QALYs | 1094 (–562; 2749) | –0.02 (–0.07; 0.03) | –66845 | 21% | 5% | 8% | 65% | 0.14 | 0.12 |
| QALYs (visual analogue scale) | 1094 (–562; 2749) | –0.01 (–0.04; 0.03) | –180324 | 30% | 7% | 7% | 57% | 0.14 | 0.36 |

ICER, incremental cost-effectiveness ratio (i.e. incremental costs in EUR per unit of benefit); QALY, quality-adjusted life-year.
*Probability HypoAware is cost-effective in comparison with usual care.

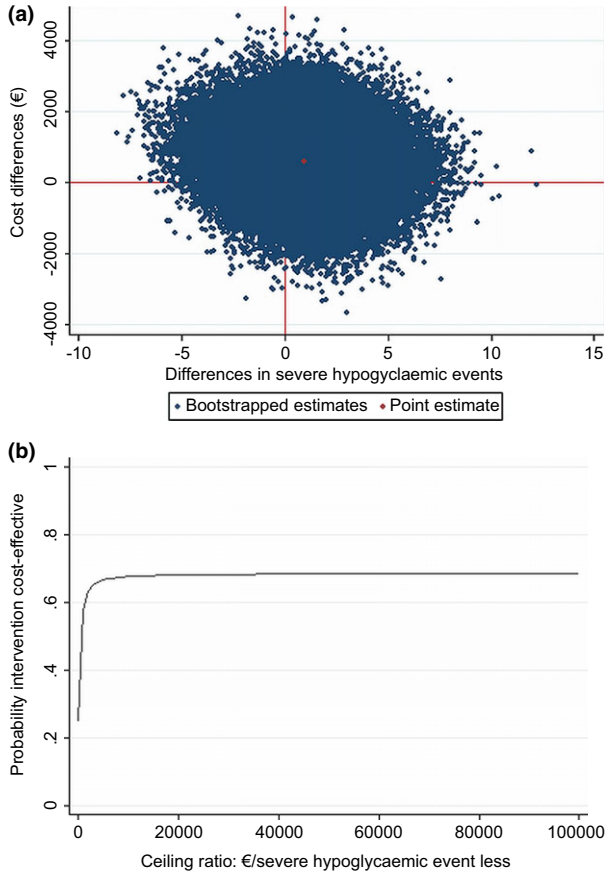


**FIGURE 1** Number of severe hypoglycaemic events prevented. (a) Cost-effectiveness plane: differences in effects between HypoAware and usual care (*x*-axis) vs differences in costs between HypoAware and usual care (*y*-axis). (b) Cost-effectiveness applicability curve: the probability of cost-effectiveness of HypoAware in comparison with usual care (*y*-axis) at different ceiling ratios (*x*-axis).

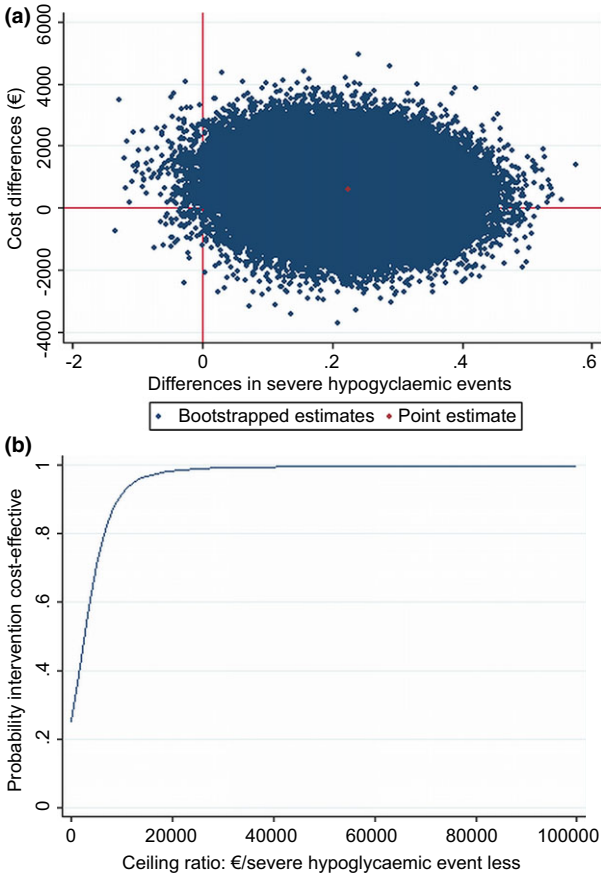


**FIGURE 2** Proportion of participants with a severe hypoglycaemic event prevented (a) Cost-effectiveness plane: differences in effects between HypoAware and usual care (*x*-axis) vs differences in costs between HypoAware and usual care (*y*-axis). (b) Cost-effectiveness applicability curve: probability of cost-effectivess of HypoAware in comparison with usual care (*y*-axis) at different ceiling ratios (*x*-axis).

95% CIs around costs (e.g. mean difference in total societal costs EUR708, 95% CI –951 to 2,298) reflect the skewed distribution of costs, meaning that much larger sample sizes are needed to get a precise estimate than for clinical effects. Sample size calculations in the present study were performed for the main effectiveness analyses [30]. In addition, we did not include a severely affected group in terms of hypoglycaemia. This could also have affected the 95% CIs.

The difference in societal costs between the two groups was mainly caused by the difference in costs of absenteeism from unpaid work between the two groups. Although the percentage of people with a paid job was slightly higher in the usual care group (56%) than in the intervention group (52%), we cannot adequately explain this difference in costs between groups. The difference in diabetes costs is mainly a result of higher use of real-time continuous glucose monitoring (CGM) in the control group. Real-time CGM use was not an exclusion criterion in the present study because standard Dutch diabetes care at the time of the study did not include the use of real-time CGM for people at risk of hypoglycaemia. The fact that the use of real-time CGM was three times higher in the usual care group suggests that it was used by participants to reduce problematic hypoglycaemia in the absence of the HypoAware intervention. A recent study demonstrated that real-time CGM is effective in lowering the risk of hypoglycaemia in Type 1 diabetes [31], which has led to accepting hypoglycaemia as an indication for reimbursement. Comparing cost-effectiveness of HypoAware and real-time CGM would be an interesting next step.

The differences observed between a societal and healthcare perspective pose a dilemma. While the Dutch Care Institute recommends analyses from a societal perspective to make recommendations for reimbursements, NICE recommends analyses from a healthcare perspective. One could argue that when people are willing to pay for informal care and loss of productivity costs themselves (in this case unpaid work), then HypoAware would be more promising; however, this would appear to require a political rather than a scientific discussion, with different outcomes in different countries.

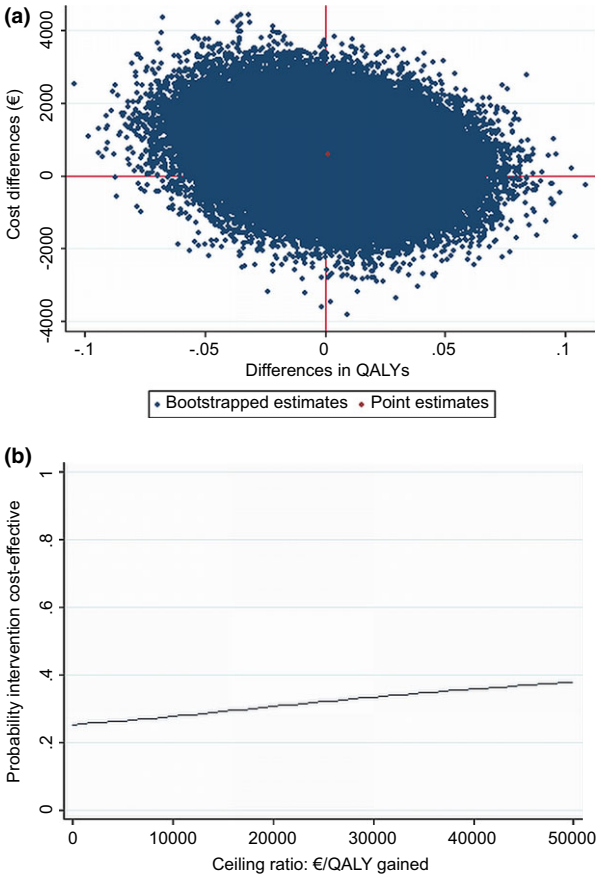


**FIGURE 3** Quality-adjusted life-years. (a) Cost-effectiveness plane: differences in effects between HypoAware and usual care (*x*-axis) vs differences in costs between HypoAware and usual care (*y*-axis). (b) Cost-effectiveness applicability curve: probability of cost utility of HypoAware in comparison with usual care (*y*-axis) at different ceiling ratios (*x*-axis). QALY, quality-adjusted life-year.

The present study is the first to evaluate the cost-effectiveness of a psycho-educational programme based on BGAT; therefore, we cannot directly compare our results with other studies. A recent study evaluated the cost-effectiveness of a general psycho-educational training [Dose Adjustment for Normal Eating (DAFNE)] in comparison with no training for people with Type 1 diabetes from a National Health Service perspective, and concluded that there was a 54% probability that DAFNE was cost-effective at a willingness to pay of GBP20,000 (approximately EUR22,000) per QALY [32]. In comparison, in the present analysis we found, from the healthcare perspective, a 60% probability at a willingness to pay of EUR20,000/QALY.

The present study has some limitations. Firstly, for the assessment of severe hypoglycaemic events we relied on self-report. However, there is evidence that supports the reliability of self-reported severe hypoglycaemia [33] and the use of objective measures (glucose sensors) are costly. Secondly, a follow-up period of 6 months is relatively short to demonstrate a reduction in severe hypoglycaemic events and associated costs, and longer-term research is therefore warranted. Based on previous BGAT research and our own RCT, however, we would expect the effects at 6 months to be maintained until at least 1 year post intervention [10,12]. Thirdly, we used the EQ-5D-5L, a generic and non-event related measure quality of life. This instrument has, however, been shown to be valid and reliable [34], and a previous study showed that fear of hypoglycaemia is adequately picked up by the dimension 'Anxiety/Depression' [35]. Our QALY estimates show that study participants experienced a substantial decrease in quality of life (mean score 0.34 as compared with a best possible score of 0.5); however, there was no substantial difference (–0.001) in QALYs between the groups, despite the higher number of hypoglycaemic events in the usual care group as compared with the HypoAware group. This leads to very large ICERs that are sensitive to the difference in costs. Finally, while carers/partners of participants were invited to the last group session of the HypoAware intervention, we did not include them in the data collection and were thus not able to assess the associated change in costs. This might be valuable to add in future studies.

The strengths of the present study include the multicentre cluster-randomized design, and the testing of the intervention in a real-life setting in a representative sample, i.e. a mix of people with Type 1 and Type 2 diabetes at risk of severe hypoglycaemia. Moreover, costs were measured from a societal and healthcare perspective, meaning that all relevant costs were included and that shifts of costs between sectors can be identified.

In conclusion, based on the results of this study, HypoAware cannot be considered cost-effective from a societal perspective. Further research in less well-resourced settings and more severely affected patients is warranted.

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### Competing interests

None declared.

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